Claims 1-75 stand provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of copending application no. 09/082,624. Examiner is hereby informed that copending application 09/082,624 is now abandoned rendering the provisional rejection moot.

Claims 3 and 54 stand rejected under 35 U.S.C. §112, first paragraph, on the basis that the specification allegedly fails to describe the claimed invention. As best understood, the Office Action appears to assert that the specification does not enable the breadth of the claims because the oligonucleotides described in Tables 1-6 of the specification:

> do not include every conceivable oligonucleotide which 'modulates the expression of a cellular adhesion protein, modulates a rate of cellular proliferation, or has biological activity against eukaryotic pathogens or retroviruses.'

Office Action at page 3. However, it is not incumbent upon an applicant for a patent to provide exemplification of "every conceivable" embodiment of a claimed invention. Indeed, a patent specification need not contain even a single working example. *In re Borkowski*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Contrary to the assertion of the Office Action, Applicants' detailed specification provides a full teaching that is more than sufficient to allow those of skill in the art to practice the claimed invention. The invention of claim 3 is directed to pharmaceutical compositions comprising at least one oligonucleotide in an emulsion, and the invention of claim 54 is directed to pharmaceutical compositions comprising an oligonucleotide in an oral dosage form. Such emulsions and oral dosage forms are described in the specification, as are methodologies for the preparation of oligonucleotides. The Office Action has not provided any evidence that those of skill in the art would be unable to prepare the claimed compositions. Rather, the Office Action appears to object to Applicants use of prophetic teachings, requiring instead that the specification set forth the specific sequence of each and every possible target for the antisense oligonucleotides of the invention. However, with respect, this is not a proper basis for rejection.

It is settled law that a specification is presumed to be enabling, and it is the PTO that has the burden of establishing a *prima facie* case of lack of enablement. *e.g.*, *In re Angstadt*, 190 U.S.P.Q.

214, 219 (C.C.P.A. 1976); *In re Marzocchi*, 169 U.S.P.Q. 367, 369-70 (C.C.P.A. 1971). To make such a *prima facie* case, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation may be necessary does not negate enablement so long as undue experimentation is not required, and the burden is on the PTO to establish that such experimentation would be undue. *Angstadt*, 190 U.S.P.Q. at 219; *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The Office Action has provided no reason of record why those skilled in the art would be unable to ascertain suitable target sequences, given the detailed teaching of the specification. Indeed, the Office Action itself admits that "oligonucleotides particularly antisense molecules and ribozymes" can be designed from "knowledge of the target sequence." Office Action at page 3-4. Because the Office Action has provided no reason of record why the skilled artisan would be unable to make and use the compounds of the invention, Applicants assert that the PTO has failed to meet its burden to establish a *prima facie* case of lack of enablement. In light of the foregoing, Applicants respectfully request withdrawal of the rejection of Claims 3 and 54 under § 112, first paragraph.

Claims 1-83 stand rejected under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable a person skilled in the art to practice the invention commensurate in scope with the claims. As best understood, the Office Action appears to assert that to the extent that the claims encompass antisense oligonucleotides, the specification does not provide enablement for modulation of expression of a cellular adhesion protein, modulation of a rate of cellular proliferation, or modulation of the biological activity of eukaryotic pathogens or retroviruses because the specification allegedly does not teach increasing expression or biological activity. Applicants respectfully disagree with the Office Action.

Applicants first note that the claims include, but are not limited, to antisense oligonucleotides. Applicants assert that target proteins can be modulated using antisense mechanisms either by directly, for example by inhibiting the synthesis of the target protein (and thus

decreasing the amount of target protein) , or indirectly, for example by inhibiting the synthesis of proteins which are agonists of, or which catabolize, the target protein. Thus, contrary to the assertion of the Office Action, antisense oligonucleotides can be used to "modulate" target proteins.

The Office Action also asserts that the specification does not reasonably provide enablement for modulation of expression of a cellular adhesion protein, modulation of a rate of cellular proliferation, and modulation of the biological activity of eukaryotic pathogens or retroviruses *in vivo*, apparently on the bases that delivery of antisense oligonucleotides is unpredictable. Applicants respectfully disagree.

Contrary to the assertion of the Office Action, the delivery of antisense molecules *in vivo* is not unpredictable. Clinical studies have shown that antisense molecules reach their intended target cells, are taken up by those target cells, and are effective. For example, attached hereto as Exhibit A is a table listing a series of antisense compounds which have been shown to have *in vivo* activity in clinical trials. Exhibit A also contains a graph of clinical data showing that the intravenous administration of 2'-methoxy-ethoxy ("MOE") antisense molecules (ISIS 11159; ISIS 18268; and ISIS 16952) are taken up by various organ tissue, further supporting the ability of antisense oligonucleotides to effectively target specific organs.

Applicants note that the Office Action relies on various general statements allegedly made by Drs. Crooke, Branch and Gura to support the contention that a person of ordinary skill in the art would be unable to practice the present invention without undue experimentation due to the "known unpredictability" of the *in vivo* delivery of antisense molecules. However, these statements are of a general nature, and appear to be taken out of context. For example, the Office Action refers to a statement by Dr. Crooke, that "extrapolations from *in vitro* uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate." However, this statement was taken completely out of context, and in fact, contrary to the premise of the Office Action, refers to the observation that the uptake of antisense molecules is more effective *in vivo* than *in vitro*.

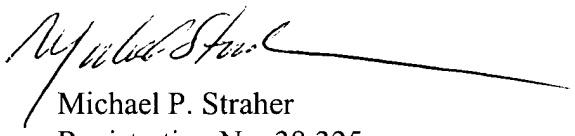
The Office Action appears to assert that insufficient guidance is provided regarding the "secondary effects" described above, appearing to require that Applicants provide a complete clinical trial for each embodiment of their claimed invention. As discussed above, however, there is no such requirement in the patent laws.

Applicants have provided a detailed specification that teaches those of skill in the art how to make and use the claimed compositions, including details regarding the delivery of antisense molecules to target cells *in vivo*. For example, the compounds molecules of the present invention are disclosed to be administrable by buccal, sublingual, endoscopic, rectal, oral, vaginal, topical, nasal, ocular, pulmonary, and urethral routes in the specification at page 4, lines 6-12 and page 9, line 27- page 10, line 4. Further, Example 8 (page 76, line 27- page 77, line 15) and Example 11 (page 86, line 7- page 88, line 6) describe specific methodology for *in vivo* intrajejunum instillation of emulsion formulations according to the present invention; Example 8 (page 77, line 16- page 79, line 5) describes the rectal administration of emulsion formulations of the present invention; Example 14 (page 93, line 7- page 95, line 31) describes enema formulations to be delivered rectally; and Example 15 (page 95, line 32- page 100, line 20) describes a method for forming a tablet to be administered orally. The Office Action has not provided any reasoning why this detailed teaching would not enable those of skill in the art to practice the claimed invention. Because the Office Action has not provided any such reasoning, Applicants' specification must be deemed enabling, and this rejection under 35 U.S.C. §112, first paragraph, is improper. Applicants therefore respectfully request withdrawal of this rejection.

Accordingly, it is respectfully submitted that this application is now in condition for

allowance. Accordingly, an indication of allowability and an early Notice of Allowance are requested.

Respectfully submitted,



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